

Obstetric causes of AKI

By

Dr. Ahmed Abdallah

Lecturer of Internal Medicine & Nephrology

Cairo University

Agenda

- Renal changes during pregnancy
- Definition
- Incidence
- Causes
- Evaluation
- Management
- Take home message

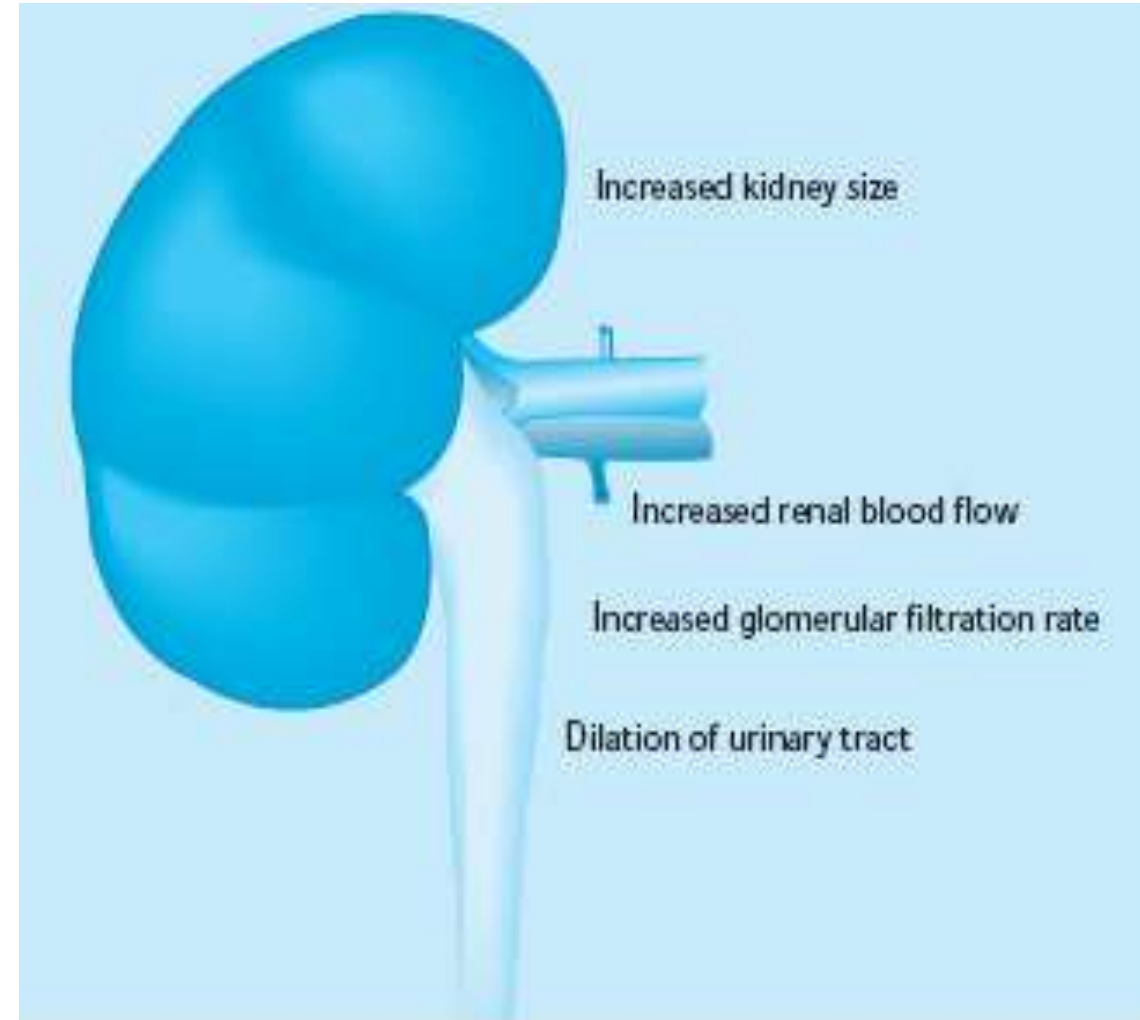
Renal changes during pregnancy

1) Anatomic changes

1- **Kidney size increases** by about 1-1.5 cm (mainly in the collecting system).

2- **Dilatation of the ureters and pelvis** (progesterone effect).

- These changes may persist for up to **12 weeks post-partum**.



2) Hemodynamic and physiologic changes

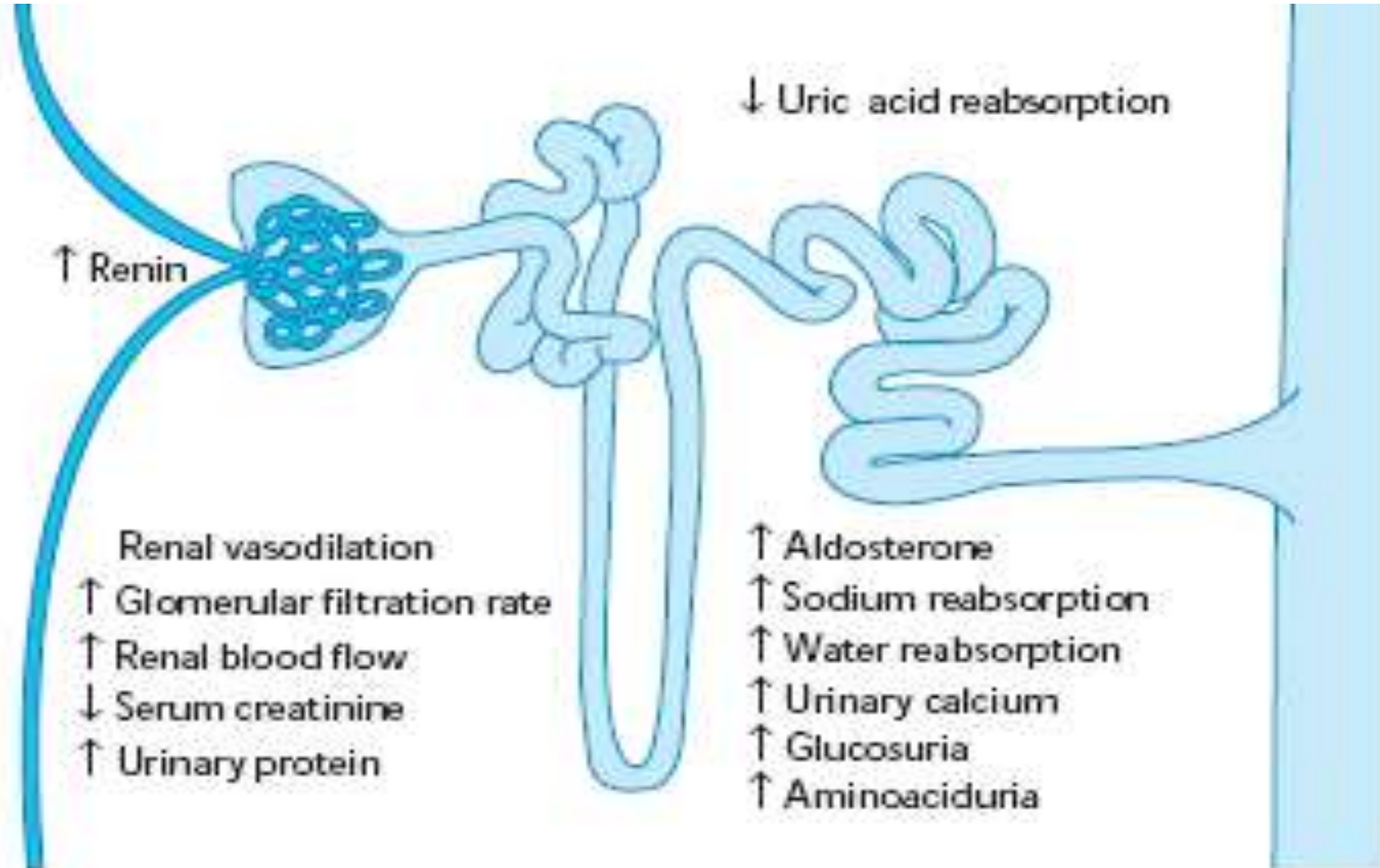
- **Renal plasma flow increases** up to 85% in the 2nd trimester due to an increase in the cardiac output and increased renal vasodilation of the afferent and efferent arterioles.
- **GFR increases** immediately after conception to about 50% above baseline in the 2nd trimester and then falls about 20% in the last trimester.
- **BP falls shortly after conception** due to peripheral VD, mediated by NO synthesis and relaxin, and a resistance to the action of ATII.
- There is a **compensatory increase in HR** and **activation of the RAAS**.
- **Blood volume increases** by 20%, and **sodium retention** of up to 900 mEq occurs. Although **edema** may therefore be benign in pregnancy, BP > 120/80 mm Hg is not normal.

- **The normal serum creatinine level falls**, so any value > 0.8 mg/dl should be considered abnormal. Similarly, **the value for BUN falls**.
- The osmotic threshold for ADH resets downward, leading to **lower serum Na^+ values** a **decline of the plasma osmolarity** (about 10 mOsm/L).
- **Increased serum aldosterone levels without hypokalemia** (competitive action of progesterone that connects to the mineralocorticoid receptors located in the distal portions of the nephron).
- The serum concentration of **chlorine** does not change.
- The higher GFR increases urate clearance, **lowering serum uric acid values**.
- Increased ventilation causes a **chronic respiratory alkalosis**.

3) Urinary abnormalities

- Up to **300 mg /day of proteinuria** can be normal in pregnancy.
(Urinary PC ratio may not be accurate in pregnancy and proteinuria quantification by 24-hour urine collection is the gold standard.)
- **Bacteriuria** is more likely to occur. Asymptomatic bacteriuria can evolve into pyelonephritis in about 1/3 of cases and should always be treated (3-day course of amoxicillin, a cephalosporin, or nitrofurantoin).
- Often there is **hypercalciuria**, explained by an increase of the GFR and of the calcium GI absorption due to a rise in 1,25-dihydroxyvitamin D3 levels.
- The filtered load of glucose increases, which may result in **renal glycosuria**.

Normal Renal Alterations in Pregnancy



Normal laboratory values in pregnancy.

| | |
|---------------------------------|----------|
| BUN mg/dL | 7–10 |
| Creatinine, mg/dL | 0.3–0.6 |
| Creatinine clearance, mL/minute | 150–200 |
| Uric acid, mg/dL | 3.2–4 |
| Sodium, mEq/L | 130–135 |
| 24-hour urine protein, mg | 300 |
| Arterial pH | 7.4–7.45 |
| Pco ₂ , mm Hg | 27–32 |
| HCO ₃ , mEq/L | 18–21 |

Definition

- **No separate definition** of AKI has been validated for pregnancy.
- The use of the **RIFLE classification** is **not consensual** and further studies are necessary to demonstrate its usefulness in pregnant women.
- **MDRD** and **Cockcroft-Gault formulas** are inaccurate for the assessment of GFR in pregnant women (the 1st **underestimates** the real GFR value, while the 2nd **overestimates** it).
- **A creatinine level of ≥ 1 mg/dL** or **a rapid rise** (by definition, in 48 hours) of 0.5 mg/dL above baseline should trigger evaluation for AKI.
- Thus, **creatinine clearance by 24-hour urine collection** remains the gold standard method for estimating GFR in pregnancy (identification of an important compromise of renal function even in the presence of normal serum creatinine).

Incidence

- AKI is one of the most challenging and serious complications of pregnancy. The reported incidence of obstetric AKI in the **developed** countries is **1-2.8%**, while in **developing** countries it is **9-25%**.

Davison J. Renal complications that may occur in pregnancy: **The Oxford Text Book of Clinical Nephrology**. 3rd ed, Vol. 15. Oxford: Oxford University Press; **2005**. p. 2233-42

- **AKI that requires dialysis** is rare in **developed** countries, with an incidence of **1:20,000 or less**, of all gestations.

Pertuiset N, Grünfeld JP. Acute renal failure in pregnancy. **Baillieres Clin Obstet Gynaecol** **1994**; 8:333-51.

Schrier RW. Diseases of Kidney & Urinary Tract. Philadelphia: **Lippincott Williams & Wilkins**; **2001**.

- The incidence of pregnancy-related AKI in **developing** countries like India is **up to 25%**, and this has not changed significantly and continues to remain an important medical problem.

Prakash J, Tripathi K, Malhotra V, Kumar O, Srivastava PK. Acute renal failure in eastern India. **Nephrol Dial Transplant** **1995**;10:2009-12.

Causes

In early pregnancy

- Prerenal
- ATN
- Renal cortical necrosis
- Pyelonephritis
- TTP

In late pregnancy

- Preeclampsia/ HELLP
- Acute fatty liver of pregnancy
- Hemolytic-uremic syndrome

In early pregnancy

1- Prerenal

1- Hyperemesis gravidarum

- History of persistent vomiting and is typically associated with metabolic alkalosis.
- Treatment consists of antiemetic therapy and volume replacement with IV normal saline and often potassium.

2- Less commonly, **hemorrhage** associated with **spontaneous abortion** can also result in prerenal azotemia.

2- ATN

- Causes:

- 1- Severe volume depletion associated with **hyperemesis gravidarum**.
- 2- **Hemorrhage** from spontaneous abortion.
- 3- Shock secondary to **septic abortion** (most commonly due to gram-negative sepsis, primarily *E. coli*).

- Diagnosis: ATN should be suspected in the setting of septic abortion, and the diagnosis can be confirmed by urine analysis showing **granular casts**, and urinary indices with an **elevated FENa⁺**.

- Treatment: **fluid resuscitation** and **pressors** for hypotension; **antibiotics**; and, if necessary, **dialysis**.

3- Renal cortical necrosis

- A **rare** cause of severe AKI.
- More likely to occur in **older** women, **multigravidas**, and **multiple** gestations following an **obstetric catastrophe**, such as abruptio placentae or septic abortion.
- **Primary DIC** in the setting of **severe renal ischemia** is the most likely initiating event.
- Presents as **gross hematuria**, **flank pain**, and **severe oliguria/anuria**.
- The diagnosis can usually be confirmed by demonstrating **a radiolucent rim in the cortex on CT scans**.
- Recovery, if it occurs, typically requires months and **renal functional recovery is usually incomplete**.

4- Acute pyelonephritis

- Acute pyelonephritis in pregnancy may result in a **reduced GFR** that can be **reversed** with treatment of the underlying infection.
- Most commonly occurs during the **second trimester**, with the predominant pathogenic organism being ***E. coli***.
- Treatment often requires **hospitalization** and the administration of **IV antibiotics** and **IV fluid** administration. **Ceftriaxone** is an appropriate choice for initial therapy.

In late pregnancy

1- Preeclampsia

- There are 4 major hypertensive disorders related to pregnancy :
- 1) **Preeclampsia**: new onset of **HTN** and **proteinuria** after **20 weeks** of gestation in a previously normotensive woman. **Eclampsia** refers to the development of grand mal seizures in a woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure.
 - 1) **Chronic/preexisting hypertension**: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg that **antedates** pregnancy or is present **before** the 20th week of pregnancy (on at least two occasions) or **persists** > 12 weeks postpartum.

3) Preeclampsia superimposed upon chronic/preexisting hypertension: new onset of **proteinuria after 20 weeks** of gestation in a woman with **chronic/preexisting HTN**. For women with chronic/preexisting hypertension who have proteinuria prior to or in early pregnancy, superimposed preeclampsia is defined by worsening or resistant HTN (especially acutely) in the last half of pregnancy or development of signs/symptoms of severe preeclampsia.

4) Gestational hypertension: HTN **without proteinuria** or other signs/symptoms of preeclampsia that develops **after 20 weeks** of gestation. It should resolve by 12 weeks postpartum. If HTN persists beyond 12 weeks postpartum, the diagnosis is revised to chronic/preexisting HTN that was masked by the physiologic decrease in BP that occurs in early pregnancy.

- **Placental underperfusion**, hypoxia, and/or ischemia.
- Release of circulating **antiangiogenic factors** (soluble fms-like tyrosine kinase [**sFlt-1**], soluble endoglin [**sEng**]) and other substances.
- Widespread maternal systemic **endothelial dysfunction** (increased vascular permeability, VC, activation of coagulation system, microangiopathic hemolysis).

Renal manifestations

1- Proteinuria

- **≥0.3 grams protein** in a 24-hour urine specimen or persistent 1+ (30 mg/dL) on dipstick or a random protein:creatinine ratio >30 mg/mmol.
- Impaired integrity of the **glomerular** barrier and altered **tubular** handling of filtered proteins (hypofiltration) leading to increased protein excretion.
- Using special studies, **podocyuria** (urinary excretion of podocytes) has been observed. It may indicate podocyte loss from the glomerulus, which may lead to a disruption of the glomerular filtration barrier and consequent proteinuria.

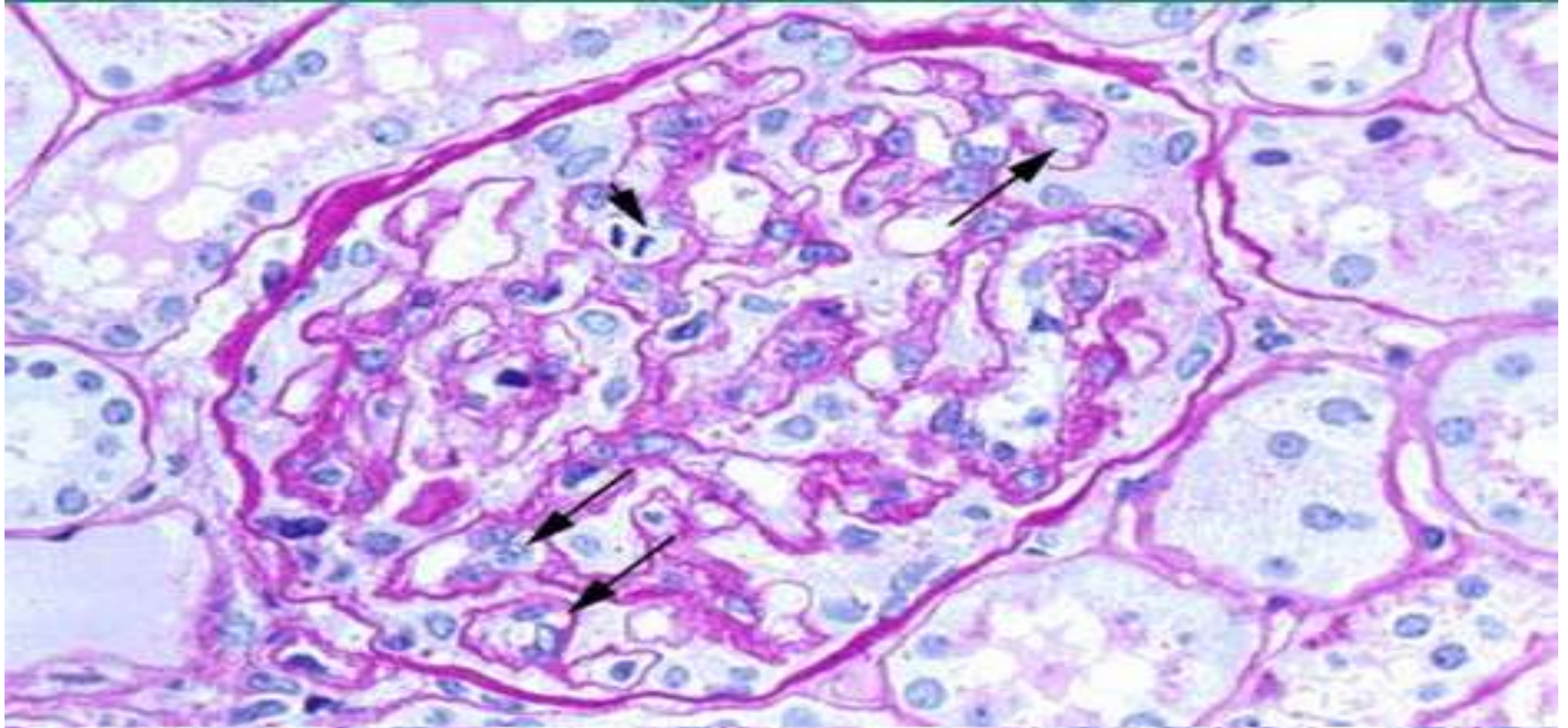
2-Renal function

- **GFR** decreases by 30 to 40 %; renal plasma flow also decreases, but to a lesser degree.
- The plasma **creatinine** concentration is generally normal or only slightly elevated (1.0 to 1.5 mg/dL). A rising creatinine and oliguria, i.e., urine output <500 mL/24 hours, indicates severe disease.
- **Hyperuricemia** and **hypocalciuria**; increased proximal sodium resorption and, secondarily, urate reabsorption induced by renal ischemia. Other possible mechanisms for hyperuricemia in preeclampsia include underlying metabolic syndrome, tissue damage, oxidative stress, and inflammation.

3- **The urine sediment** is typically benign.

4- **The renal histology**: 'glomerular endotheliosis.'

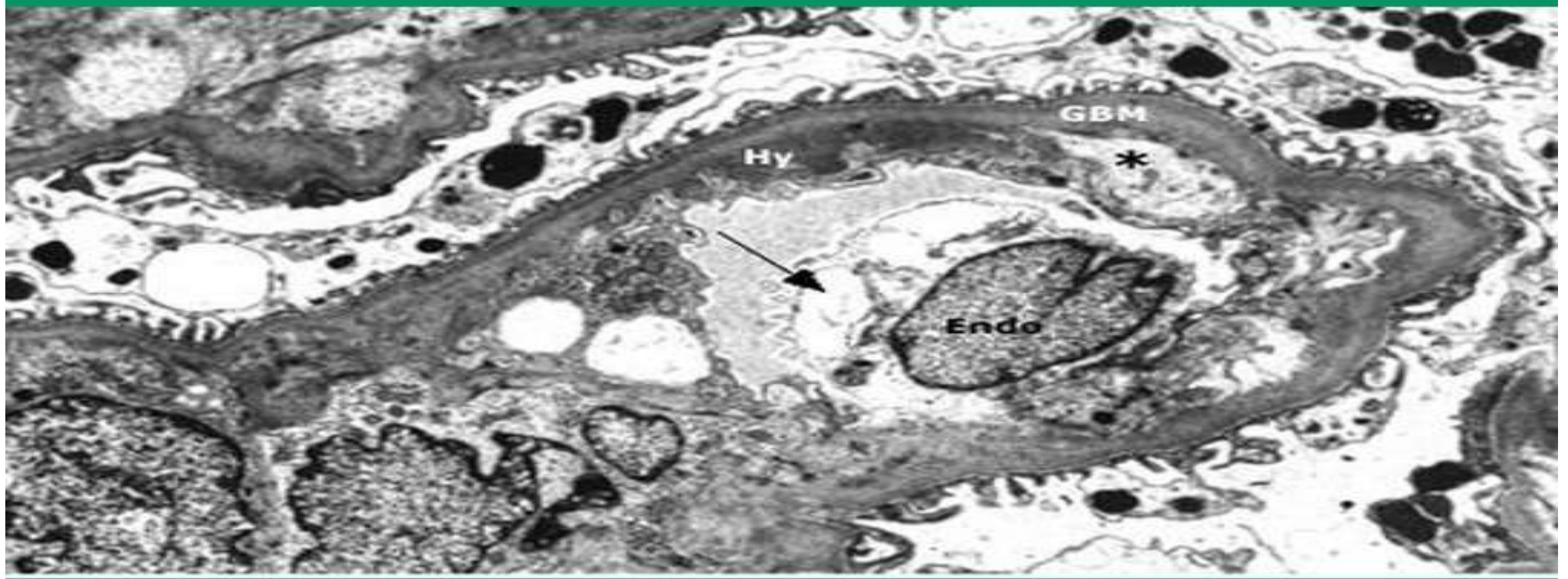
- Endothelial cell swelling
- Loss of fenestrations
- Occlusion of capillary lumens
- Foot process effacement is not a prominent feature, despite marked proteinuria.



Light micrograph in preeclampsia showing glomerular endotheliosis. The primary changes are swelling of damaged endothelial cells, leading to partial closure of many of the capillary lumens (large arrows). Mitosis within an endothelial cell (small arrow) is a sign of cellular repair.

Courtesy of Helmut Rennke, MD.

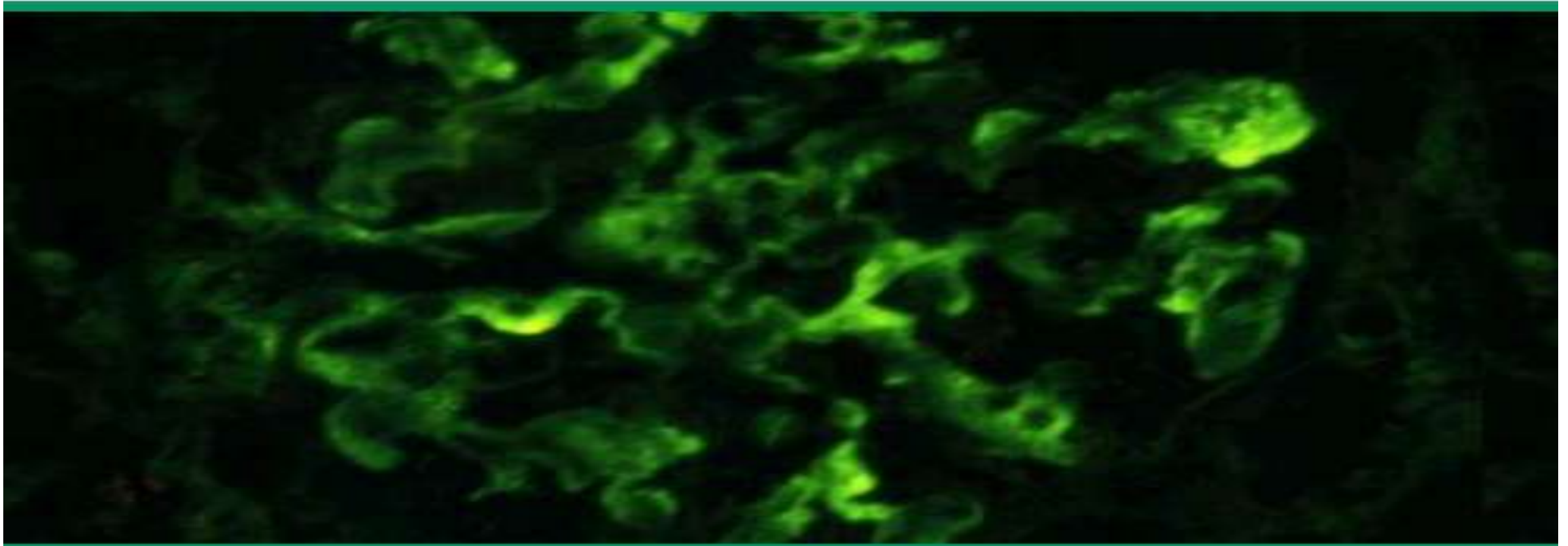
Preeclampsia



Electron micrograph in preeclampsia showing narrowing of the capillary lumen due to expansion of the mesangium, swelling of the endothelial (Endo) cell cytoplasm (arrow), and subendothelial deposition of hyaline (Hy) material which represents large macromolecules such as IgM. The damaged endothelial cell has become partially separated (*) from the glomerular basement membrane (GBM).

Courtesy of Helmut Rennke, MD.

IgM deposition in preeclampsia



Immunofluorescence microscopy in preeclampsia showing diffuse IgM deposition. This represents nonspecific entrapment of larger proteins in the more permeable glomerular capillary wall, rather than the formation of discrete immune complexes. There is, for example, generally no deposition of IgG.

Courtesy of Helmut Rennke, MD.

2- HELLP

- **Represents a severe form of preeclampsia**, but this relationship remains **controversial**.
- As many as 15 to 20 % of affected patients do not have antecedent hypertension or proteinuria, leading some experts to believe that HELLP is a **separate disorder from preeclampsia**.
- Both severe preeclampsia and HELLP syndrome may be associated with other **hepatic** manifestations, including infarction, hemorrhage, and rupture.

- Symptoms typically develop in the **third** trimester, but 2nd trimester or postpartum disease is also possible.

1- The most common clinical presentation is **abdominal pain and tenderness** in the midepigastrium, right upper quadrant, or below the sternum.

2- Many patients also have **nausea, vomiting, and malaise**, which may be mistaken for a nonspecific viral illness or viral hepatitis.

3- **Hypertension** and **proteinuria** are present in approximately 85 % of cases, but it is important to remember that either or both may be absent in women with otherwise severe HELLP syndrome.

4- **DIC, abruptio placentae, AKI, pulmonary edema, subcapsular liver hematoma, and retinal detachment.** **Jaundice** and **ascites** may also be present.

5- **Bleeding** related to thrombocytopenia is an **uncommon** presentation.

6- Some patients are **asymptomatic**.

- **All of the following criteria are required to diagnose HELLP:**

1- **MAHA** with characteristic schistocytes on blood smear. Other signs suggestive of hemolysis include an elevated indirect bilirubin and a low serum haptoglobin concentration (≤ 25 mg/dL).

2- **Platelet** count $\leq 100,000$ cells/microL

3- Total **bilirubin** ≥ 1.2 mg/dL

4- Serum **AST** ≥ 70 IU/L. Some investigators obtain ALT levels instead of, or in addition to, AST levels. An advantage of the AST is that it is a single test that reflects both hepatocellular necrosis and red cell hemolysis.

- Women who do not meet all of the above laboratory abnormalities are considered to have **partial HELLP syndrome**. These patients may progress to complete expression of HELLP syndrome.

Management recommendations

- Severe maternal disease (e.g., multiorgan dysfunction, DIC, liver infarction or hemorrhage, renal failure, abruptio placenta) or nonreassuring fetal status is an indication for **prompt delivery regardless of gestational age**.
- For pregnancies **≥34 weeks** of gestation, we recommend delivery rather than expectant management ([Grade 1C](#)). In this population, the potential risks of preterm birth are outweighed by the risks associated with HELLP syndrome.
- For pregnancies **< 34 weeks** of gestation in which maternal and fetal status is reassuring, we suggest delivery after **a course of glucocorticoids** to accelerate fetal pulmonary maturity rather than expectant management or prompt delivery ([Grade 2C](#)). Although the laboratory abnormalities of HELLP syndrome will reverse in a subgroup of patients managed expectantly and serious maternal complications are uncommon with careful maternal monitoring, there is no high quality evidence showing that overall perinatal outcome is improved with expectant management.
- For gestations **< 30 to 32 weeks** with an unfavorable cervix, we suggest C.S to avoid a potentially long induction ([Grade 2C](#)).
- We recommend not giving [dexamethasone](#) for treatment of HELLP syndrome ([Grade 1B](#)). Dexamethasone does not accelerate resolution of laboratory abnormalities or reduce the risk of maternal complications.

3- AFLP

- **A disorder which is unique to human pregnancy, characterized by microvesicular fatty infiltration of hepatocytes.**
- **It was described in 1940.**
- **AFLP is rare with an approximate incidence of 1 in 7000 to 1 in 20,000 deliveries.**
- **It is more common with multiple gestations and possibly in women who are underweight.**

- **Inherited defects in mitochondrial beta-oxidation of fatty acids,** long-chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD).
- The LCHAD catalyzes the third step in the beta-oxidation of fatty acids in mitochondria (the formation of 3-ketoacyl-CoA from 3-hydroxyacyl-CoA).
- **The accumulation of long-chain 3-hydroxyacyl metabolites produced by the fetus or placenta is toxic to the liver** and may be the cause of the liver disease.

- The most frequent initial symptoms are **nausea or vomiting** (approximately 75 % of patients), **abdominal pain** (particularly epigastric, 50 %), **anorexia**, and **jaundice**.
- About 50% of patients have **signs of preeclampsia** at presentation or at some time during the course of illness.
- **Transient polyuria and polydipsia** due to central DI also can be seen; (the mechanism is unknown).
- Rare patients develop **pancreatitis**, which can be severe.

- Serum **aminotransferase elevations** ranging from modest values up to 1000 IU/L.
- Serum **bilirubin** levels are also usually elevated.
- The **TLC** may be higher than is usually seen in pregnancy (nonspecific).
- The **platelet count** may be decreased with or without other signs of DIC which is associated with marked reduction in **antithrombin III**.
- Severely affected patients also have elevations in serum **ammonia**, **prolongation of PT**, and **hypoglycemia** caused by hepatic insufficiency.
- **AKI** and **hyperuricemia** are often present.

- The diagnosis is usually made **clinically** based upon the setting, presentation, and compatible **laboratory** and **imaging** results.
- Liver biopsy is **diagnostic** , it is not always performed.
- There is **no specific medical treatment**. The primary treatment is **prompt delivery**, usually emergently, after maternal stabilization.

4- TMA

- Pregnancy-associated thrombotic microangiopathies (p- TMA) are **rare**, affecting 1 per 25,000 pregnancies.
- They are defined by the presence of **fibrin and/or platelet thrombi** in the microcirculation of multiple organs.
- Depending on the most affected organ (brain or kidney), **2 clinical entities** have been described: TTP and HUS:
 - 1) **TTP** is characterized by fever, thrombocytopenia (usually severe), MAHA, mild renal failure and neurologic symptoms (disorientation, ataxia, headache, focal changes, seizures or aphasia).
 - 2) **HUS** clinical features are similar but renal involvement is more pronounced and the presence of neurologic symptoms is rare. However, the clinical manifestations of these 2 entities may overlap, so in daily practice the distinction may be difficult

- The p-TMA may occur **any time during pregnancy or at puerperium**, in previously healthy women.
- **TTP** is often diagnosed **before delivery**, especially in the second and third trimesters because the ADAMTS-13 level physiologically tends to decrease during the last trimester.
- **Atypical HUS** occurs mainly in the **first 6 months after delivery**.
- The diagnosis of p-TMA is **clinically challenging**, due to the need to exclude other specific pregnancy thrombotic diseases, such as preeclampsia and HELLP syndrome.

- The p-TMA **renal involvement is common** (**two thirds** of cases).
- Most patients have severe renal failure requiring **dialysis** therapy.
- The kidney disease results from **renal TMA** and is morphologically characterized by multiple intraluminal thrombi; double contour appearance of GBM; mesangiolysis; and arterial and arteriolar changes, including mucoid intimal thickening, fibrinoid necrosis or thrombosis.
- The **maternal mortality** in p-TMA has declined in recent years and is now between 10% and 20%.
- **High perinatal mortality rate** (30%-80%) caused mainly by growth restriction and placental infarction due to thrombosis of decidual arterioles.
- **The long-term renal outcome is poor.** Seventy-six % of patients with AKI related to p-TMA develop ESRD.

| | Severe preeclampsia | HELLP | AFLP | TTP | aHUS |
|---|----------------------------|-----------------|----------|---------------------------|------------|
| Time of diagnosis | Usually 3T | | 3T | Usually 2T/3T | Postpartum |
| Frequency of hypertension | 100% | 80% | 25%-50% | 0/+ | + |
| Fever / neurologic symptoms | no | no | no | yes | no |
| Acute kidney Injury | mild | mild / moderate | moderate | mild / moderate | severe |
| Hemolytic anemia | 0 | + | 0/+ | ++ | + |
| Thrombocytopenia | 0/+ | + | 0 | ++ | ++ |
| Liver transaminase increase | 0/+ | + | ++ | 0 | 0 |
| Partial thromboplastin time increase | 0/+ | 0/+ | + | 0 | 0 |
| ADAMTS-13 activity <10% | 0 | 0 | 0 | ++ | + |
| Recovery after delivery | 2-3 days | 1 week | 1-2 days | No recovery | |
| Treatment | Delivery; Support measures | | | Plasma infusion /exchange | |

The following conditions should also be considered

1) Obstructive uropathy

- **Moderate or severe dilatation** of the collecting system in women with **oliguria or anuria**.
- **Gravid uterus, polyhydramnios, kidney stones, and enlarged uterine fibroids** are the most likely causes.
- Usually resolves with delivery, although **ureteral stenting** may be required preterm.

2) Nephrolithiasis

- In pregnancy, 1,25 di-hydroxycholecalciferol levels are elevated due to increased production by the kidney and placenta, resulting in **hypercalciuria**.
- This results in an increased risk of **nephrolithiasis** along with an increased risk of **UTI**.
- **Ultrasonography** is the primary diagnostic imaging modality used, and ureteral stenting may be necessary if the stones cannot be passed.

3) Antiphospholipid syndrome

- Women with anticardiolipin antibodies and the lupus anticoagulant are at risk of **fetal loss** and **worsening renal function**.
- All pregnant women with SLE should be **screened** for antiphospholipid antibodies.
- Treatment with **low-dose aspirin or heparin** should be considered but depends on the antibody levels and previous obstetric history of early fetal loss and/or thrombosis.

Evaluation

History & Examination

- Age
- Smoking
- Trimester
- GI: Abdominal pain, nausea and vomiting
- Urinary: Hematuria, flank pain and urine output
- CNS: Headache, visual symptoms and convulsions
- Fever (Pyelonephritis, TTP)
- Past obstetric history
- Underlying disease e.g.DM, SLE
- Bleeding
- Petechial rash
- Drug intake
- BP
- Temperature
- Jaundice
- Hyperreflexia
- Pulmonary oedema

Investigations

1- Lab

- CBC and peripheral film (schistocytes)
- LDH, Retix and haptoglobin
- KFT (uric acid)
- LFT
- Urine analysis
- Proteinuria quantification
- ABG
- PT and PTT
- Blood glucose
- FENa⁺
- Autoimmune profile (APS and SLE), C3 and C4
- ADAMTS 13
- Fibrinogen, FDPs and D-dimer

2- Imaging

- U/S
- MRI

3- Histopathology

- Liver biopsy
- Renal biopsy

- Percutaneous renal biopsy is **usually avoided during pregnancy** because of the fear of bleeding from the bleeding site.
- Renal biopsy is indicated if there is reason to **suspect a renal disorder that may be treated successfully, especially in early pregnancy**, while permitting the pregnancy to continue:
 - LN
 - MCD
 - Immune-mediated interstitial nephritis
 - Crescentic GN
 - Some forms of vasculitis including Wegner's granulomatosis.

Management

- Almost all patients with **significant renal disease and/or hypertension** in **late pregnancy**, or when the **likelihood of fetal viability is very high**, are **delivered** and they can be managed as non-gravid patients.
- If **progressive renal failure** occurs either in **early pregnancy** or **before fetal viability** can be assured, however, **dialysis** may need to be considered.
- Dialysis should be initiated when the serum **creatinine level is 3.5-5.0** mg/dL or the **GFR is < 20 ml/min**.
- Fetal outcome is improved with longer, more frequent hemodialysis sessions, which usually involves **20 hours of dialysis per week**.
- **Daily dialysis** is more likely to prevent hypotension and significant metabolic shifts.

- Dialysis should aim to keep **BUN levels < 50 mg/dL**, because controlling uremia may avoid polyhydramnios, control hypertension, and improve the mother's nutritional status.
- **PD with smaller volumes and frequent exchanges** can also be done to achieve these same goals.
- **Anemia** should be treated with **erythropoietin** and careful attention to **iron** therapy.
- **Nutritional support** that allows weight gains of **0.3 to 0.5 kg/week** should be maintained in the **2nd and 3rd trimesters**.

Drug Therapy for Hypertension in Pregnancy

1- Alpha methyldopa is the first-line therapy for mild hypertension, based on a long record of effectiveness and safe fetal outcomes.

2- Labetalol is an effective alternative.

3- Hydralazine can be used for more severe hypertension, commonly in combination with methyldopa or beta-blockers.

4- Beta-blockers, particularly atenolol, may cause fetal bradycardia in the **1st trimester**, but these agents can be used safely later in pregnancy.

5- CCBs : it was found that patients were less likely to have persistent hypertension when **CCBs** were used, as compared with hydralazine, though there was insufficient data for comparing the effectiveness of different agents..

6- Diuretics are generally not recommended but can be continued if they are effectively controlling the patient's chronic hypertension. These drugs **should not be used in superimposed preeclampsia**.

7- ACEIs and ARBs are **contraindicated in pregnancy**, because they have been associated with increased fetal loss in animal studies; these agents have also been associated with fetal renal tubular dysplasia, oligohydramnios, perinatal acute renal failure, and other congenital anomalies.

Take home message

- **The physiologic alterations of pregnancy** have important implications for renal structure and functions, which may possibly lead to diagnostic dilemmas and wrong interpretation of various investigations carried out during the gestational period.
- **No separate definition** of AKI has been validated for pregnancy.
- The development of AKI in a pregnant patient causes particular anxiety. **The DD is broad**, and two lives are at stake.
- Clinicians should be prepared to **start dialysis early** in pregnant patients and maintain effective doses as the pregnancy continues.
- It is essential to focus on the **prevention** and **periodic evaluation** of pregnant women to improve maternal and perinatal outcomes.

THANK YOU

- The development of AKI in pregnancy is a major clinical challenge because it is necessary to consider 2 patients (mother and fetus)
- can be caused by specific pregnancy diseases not yet fully understood.
- The complexity of the AKI in pregnancy requires a multidisciplinary approach where the nephrologist plays an important role.

- Some have suggested using the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) criteria, which focuses on the percent change in creatinine or the development of oliguria, to define AKI in pregnant women, but further work to demonstrate its utility is required.



Table 2: Indications of renal biopsy during pregnancy

Sudden deterioration of renal functions at <30-32 weeks of pregnancy
with no apparent cause to rule out RPRF

Symptomatic nephrotic syndrome at <30-32 weeks of gestation – not
a universal indication

Presents with active urinary sediment not evaluated in past – to
classify lupus, to rule out scleroderma

Rapidly progressive renal failure (RPRF)

Table 2: Indications of renal biopsy during pregnancy

Sudden deterioration of renal functions at <30-32 weeks of pregnancy with no apparent cause to rule out RPRF

Symptomatic nephrotic syndrome at <30-32 weeks of gestation – not a universal indication

Presents with active urinary sediment not evaluated in past – to classify lupus, to rule out scleroderma

Rapidly progressive renal failure (RPRF)

- Imaging
- U/S
- MRI
- Histopathology
- Liver biopsy
- Renal biopsy

ACG guidelines liver disease during pregnancy

©2013 UpToDate ®

American College of Gastroenterology Guidelines: Liver disease in the pregnant patient

Use of gestational age of the pregnancy is the best guide to the differential diagnosis of liver disease in the pregnant woman

Hyperemesis gravidarum should be considered in the differential diagnosis of abnormal liver tests presenting in the first trimester

Cholestasis of pregnancy is common, and should be considered in the differential diagnosis of abnormal liver tests presenting initially in the second trimester. Affected pregnancies are at increased risk for prematurity and stillbirth, and early delivery should be considered when possible

HELLP (hemolysis, elevated liver tests, low platelets) syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis of abnormal liver tests in the second half of pregnancy, usually in the third trimester

Patients with acute fatty liver of pregnancy have true hepatic dysfunction, and may, or may not, have signs of pre-eclampsia and HELLP syndrome

Consider viral or drug-induced hepatitis, gallstone disease, or malignancy in the differential diagnosis of abnormal liver tests in any of the trimesters of pregnancy

Chronic hepatitis B or C poses a risk of transmission to the offspring

Comparison of frequency of signs, symptoms, and laboratory findings in TTP, HUS, and HELLP

| | TTP | HUS | HELLP |
|--------------------------------|---------------------|---------------------|-------|
| Abdominal pain | ++ | ++ | ++ |
| Low ADAMST13 activity | + / ++ | - | - |
| Anemia | ++ | ++ | + |
| Elevated lactic dehydrogenase | ++ very high values | ++ very high values | ++ |
| Elevated transaminases | - / + | - / + | ++ |
| Fever | + | - | - |
| Headache or visual disturbance | ++ | - | ++ |
| Hypertension | + / ++ | ++ | ++ |
| Jaundice | - | - | + |
| Nausea and vomiting | ++ | ++ | ++ |
| Proteinuria | + and hematuria | ++ | ++ |
| Thrombocytopenia | ++ | ++ | ++ |
| von Willebrand factor | ++ | ++ | - |

Reported frequency of signs and symptoms of HELLP syndrome

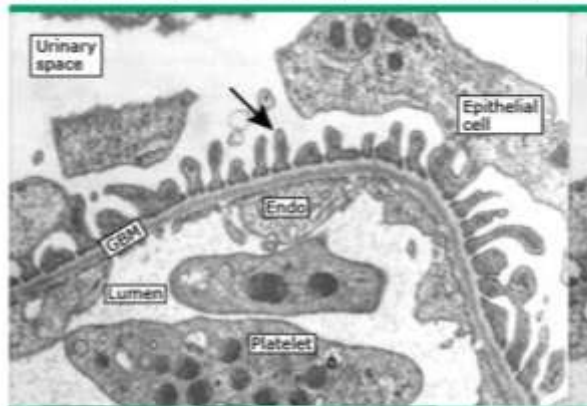
| Sign/symptom | Frequency, percent |
|--------------------------------------|--------------------|
| Proteinuria | 86 to 100 |
| Hypertension | 82 to 88 |
| Right upper quadrant/epigastric pain | 40 to 90 |
| Nausea, vomiting | 29 to 84 |
| Headache | 33 to 61 |
| Visual changes | 10 to 20 |
| Jaundice | 5 |

WHEN TO EVALUATE FOR ANTIPHOSPHOLIPID ANTIBODIES

- The American College of Obstetricians and Gynecologists (ACOG) recommends testing women with a prior unexplained arterial or venous thromboembolism, or a new arterial or venous thromboembolism during pregnancy, or a history of venous thromboembolism who have not been tested previously. Obstetric indications for antiphospholipid antibody testing include:
- One or more unexplained deaths of a morphologically normal fetus at $\geq 10^{\text{th}}$ week of gestation, or
- Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, in the absence of maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal abnormalities
- Although one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or features consistent with placental insufficiency is a clinical criterion for APS, ACOG opines that there is insufficient evidence that screening and treatment of women with these conditions improves subsequent pregnancy outcomes. Low dose ASA may be prescribed for these women whether or not aPL antibodies are present.
- ACOG recommends testing for the presence of LA, aCL (IgG and IgM), and anti-beta2-glycoprotein I (IgG and IgM). If the initial screening test is positive, it should be repeated in 12 weeks to determine whether the aPL is transient or persistent.

- The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend that women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation) be tested for the presence of LA and aCL antibodies. This has generally been accepted by both the hematology and obstetrics communities, despite the absence of clear evidence of biological plausibility and of adequately sized, prospective cohort studies in which the outcomes in a fourth pregnancy were compared between aPL positive and negative women.
- The American College of Rheumatology recommends testing for aPL in women with a history of miscarriage after 10 weeks who are considering pregnancy.

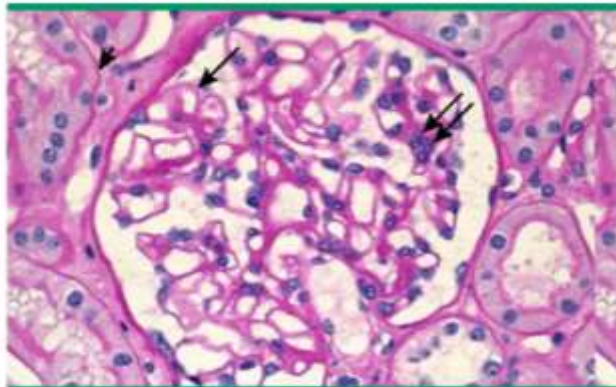
Electron micrograph of a normal glomerulus



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut Rennke, MD.

Normal glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Courtesy of Helmut G Rennke, MD.

- A standardization of GFR measurement in pregnancy is far from being reached. In 2007, 2 prospective studies were published to evaluate the accuracy of formulas for estimating GFR in pregnant women. Smith et al (13) compared the MDRD formula with inulin and creatinine clearance by 24-hour urine collection.
- On the other hand, Alper et al (14) compared both versions of the MDRD equation, the Cockcroft-Gault equation and creatinine clearance by 24-hour urine collection, in women with preeclampsia.

- AKI in pregnancy (P-AKI) remains a cause of significant fetomaternal mortality and morbidity. Its definition, and hence, its incidence, varies widely in published studies from mild increase in serum creatinine >0.8 mg/dl to dialysis requirement.

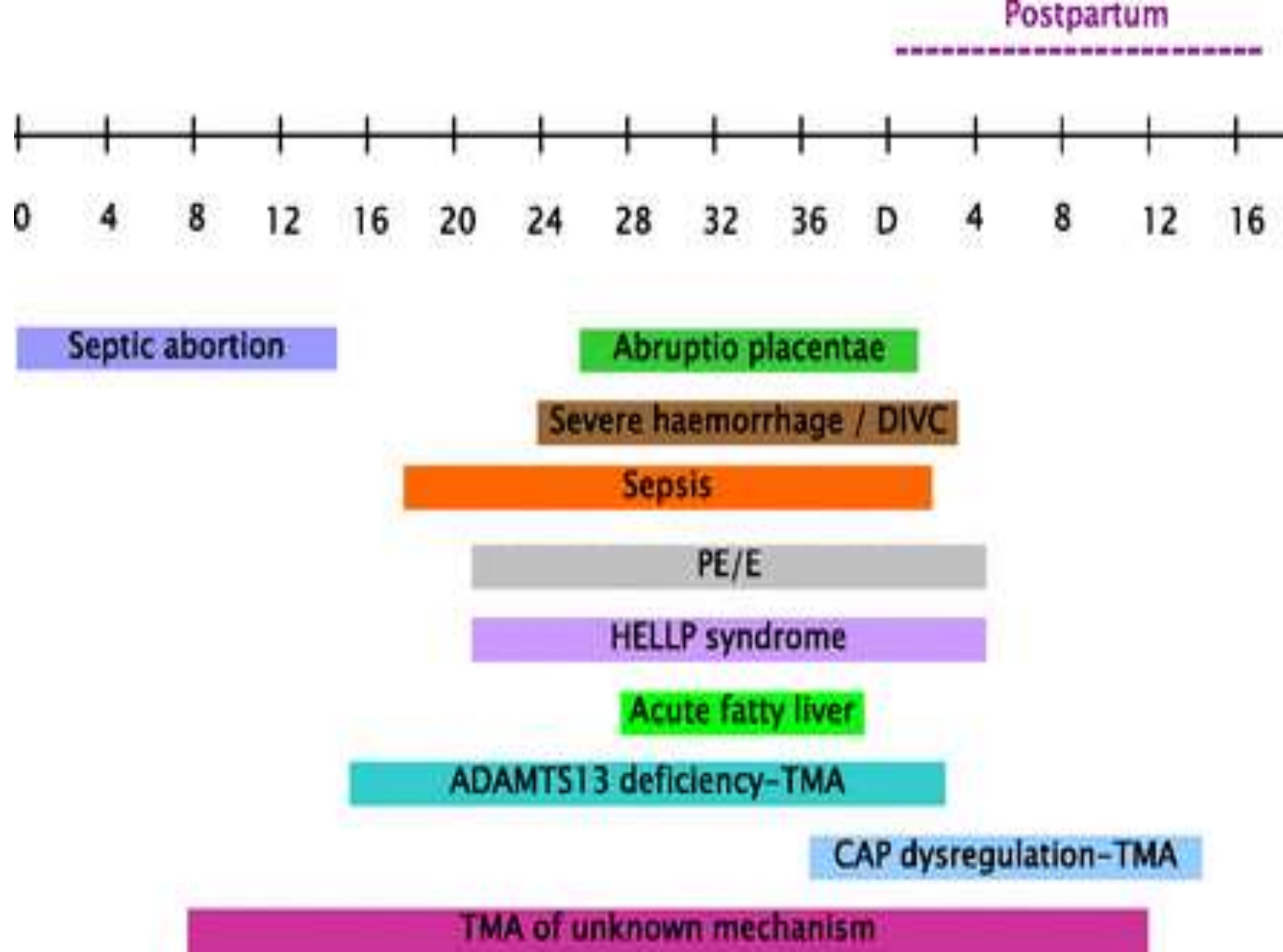
Prakash J, Niwas SS, Parekh A, Pandey LK, Sharatchandra L, Arora P, Mahapatra AK: Acute kidney injury in late pregnancy in developing countries. *Ren Fail* 32: 309–313, 2010

Mattar F, Sibai BM: Eclampsia. VIII. Risk factors for maternal morbidity. *Am J Obstet Gynecol* 182: 307–312, 2000

- However, the increase in serum creatinine may be a late event in the course of P-AKI.
- Hypertension and edema may herald the onset the P-AKI, and old (serum uric acid and proteinuria) or new currently evaluated (neutrophil gelatinaseassociated lipocalin) biologic markers may help predict the occurrence of AKI in pregnant women.

Youssef A, Righetti F, MoranoD, Rizzo N, Farina A: Uterine artery Doppler and biochemical markers (PAPP-A, PIGF, sFlt-1, Pselectin, NGAL) at 11+0 to 13+6 weeks in the prediction of late (>34 weeks) pre-eclampsia. *Prenat Diagn* 31: 1141–1146, 2011

- Fortunately, the incidence of AKI in pregnancy has fallen substantially over the past several decades, predominantly due to improved access to prenatal care and emergency services for the management of obstetric complications.
- Overall, the incidence of significant AKI in pregnancy is believed to be about 1 in 15,000 pregnancies.
- In less developed nations, though, rates of AKI related to septic abortion and other infectious and hemorrhagic complications continue to be high.



Renal biopsy and pregnancy.

Kuller JA¹, D'Andrea NM, McMahon MJ.

Author information

Abstract

OBJECTIVE: Our aim was to review our experience with renal biopsy in pregnancy.

STUDY DESIGN: We reviewed 18 renal biopsies performed during pregnancy or in the immediate postpartum period at the University of North Carolina. Indications, histopathologic findings, complications, and neonatal outcome were reviewed for each case.

RESULTS: Fifteen patients underwent biopsy during the antepartum period and 3 in the postpartum period. Only 5 patients had the classic histopathologic preeclamptic lesion glomeruloendotheliosis confirmed. There were 7 identifiable renal hematomas after biopsy; 2 patients required blood transfusion. There were 4 intrauterine fetal deaths in this series; it is presumed that none were a result of the biopsy.

CONCLUSION: Renal biopsy in pregnancy is a morbid procedure and should be considered only if it offers the opportunity to make a diagnosis other than severe preeclampsia in a patient remote from term.

Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review.

Piccoli GB¹, Daidola G, Attini R, Parisi S, Fassio F, Naretto C, Deagostini MC, Castelluccia N, Ferraresi M, Roccatello D, Todros T.

Author information

Abstract

BACKGROUND: Kidney diseases, which have a prevalence of 3% in women of childbearing age, are increasingly encountered in pregnancy. Glomerulonephritis may develop or flare up in pregnancy, and a differential diagnosis with pre-eclampsia may be impossible on clinical grounds. Use of kidney biopsy is controversial, but a systematic review has not been carried out to date.

OBJECTIVES: To review the literature on kidney biopsy in pregnancy, with a focus on indications, risks and timing.

SEARCH STRATEGY: Medline, Embase, CHINAL and the Cochrane Library were searched in September 2012, with 'pregnancy' and 'kidney biopsy' used as MESH and free terms, for the period 1980-2012. Results were filtered for 'human' if this option was available.

SELECTION CRITERIA: Biopsies during pregnancy and within 2 months after delivery. Case reports (fewer than five cases) and kidney grafts were excluded. Paper selection was performed in duplicate.

DATA COLLECTION AND ANALYSIS: Data were extracted in duplicate. The high heterogeneity in study design necessitated that the review be narrative, except for data on adverse events, which were analysed with regard to the timing of kidney biopsy.

MAIN RESULTS: Of 949 references, 39 were selected, providing data on 243 biopsies in pregnancy and 1236 after delivery (timing was unclear in 106 women). The main aims of the studies were to define morphology in pre-eclampsia (23 studies), to carry out a risk-benefit analysis of kidney biopsy (11 studies), and to investigate pregnancy-related acute kidney injury (five studies). Four cases of major bleeding complications occurred at 23-26 weeks of gestation. Relevant complications were observed in 7% of women during pregnancy and 1% after delivery ($P = 0.001$). Kidney biopsy performed for the diagnosis of glomerulonephritis or pre-eclampsia led to therapeutic changes in 66% of cases.

AUTHORS' CONCLUSIONS: The evidence on kidney biopsy in pregnancy is heterogeneous, but a significantly higher risk of complications (relative to postpartum biopsy) was found, with a possible peak at around 25 gestational weeks.

Table 4. Diagnostic tests

Shiga toxin

Stool culture for *E. coli* plus either toxicology for shiga toxin or PCR for *shiga toxin* gene

Urine culture for *E. coli*

Other bacterial testing as indicated

S. pneumoniae

T antigen expression on red cells

PCR of blood and/or secretions

Blood culture

Complement dysregulation

Plasma/serum protein levels

C3

Factor H, factor I, factor B

MCP (CD46) expression on PBMCs

Factor H autoantibodies

Mutations

Direct exon sequencing of *CFH*, *MCP*, *CFI*, *CFB*, *C3*

Copy number variation across *CFH-CFHR* locus

ADAMTS13 deficiency

ADAMTS13 activity

ADAMTS13 autoantibodies

ADAMTS13 mutations

Other associations

Pregnancy test

Table 5. Treatment

(i) Supportive measures only

Paediatric STEC-HUS and invasive pneumococcal infection (p-HUS)

Cobalamin deficiency (children), HSCT- or malignancy-associated

TMA, malignant HT

(ii) Therapeutic plasma exchange (TPE)

First exclude paediatric STEC-HUS and p-HUS

Recommended in all other settings

Including TTP and aHUS (probably of no benefit in MCP-aHUS)

Controversial in adult STEC-HUS

Plasma infusion recommended in known congenital TTP

(iii) Eculizumab

aHUS

(iv) Steroids and/or rituximab

Possibly in acquired TTP and aHUS with factor H autoantibodies

(v) Renal transplantation for ESKD

STEC-HUS

MCP-aHUS

Living-related donation contraindicated

(vi) Prophylactic strategies in high-risk transplantation (i.e. non-MCP aHUS)

Intensive perioperative TPE

Eculizumab

Rituximab (for factor H autoantibodies)

Combined kidney–liver transplantation

It is rare for renal biopsy to be required in pregnancy. After 32 weeks of gestation, if the renal state has changed so much that biopsy is considered necessary to guide treatment, it is better to deliver the baby and to manage the renal disease outside of pregnancy. Situations in which biopsy may provide information that could have a significant impact on the pregnancy outcome for mother and baby are the following:

- 1 *De novo* onset of nephrotic-range proteinuria or unexplained impaired GFR with abnormal urine sediment before fetal viability, that is, before 24 weeks of gestation. Nephrotic syndrome after this stage can generally be managed conservatively until delivery usually at about 32 weeks. Most such cases are due to preeclampsia.
- 2 Before 32 weeks of gestation when the clinician and patient have agreed that immunosuppression or plasma exchange will be used if necessary while prolonging the pregnancy to about 32 weeks: rapidly declining GFR without any ...

- Since 1960, the incidence of AKI in pregnancy has been reduced significantly, and currently affects 1 per 20,000 pregnancies (1). The legalization of abortion contributed to this decline in most developed countries, leading to a reduction in the number of septic abortions – the main cause of AKI in recent decades.
- Sodium balance is maintained by the rise of its reabsorption within the PCT and in the distal portions of the nephron (under aldosterone influence).

Differential diagnosis

| | HELLP | AFLP | TTP | HUS |
|-----------------------------|-------------------|------------------------|------------------|-----------------|
| Hypertension | 80% | 25–50% | Occasional | Present |
| Renal insufficiency | Mild to moderate | Moderate | Mild to moderate | Severe |
| Fever, neurologic symptoms | 0 | 0 | ++ | 0 |
| Onset | 3rd trimester | 3rd trimester | Any time | Postpartum |
| Platelet count | Low to very low | Low to very low | Low to very low | Low to very low |
| Liver function test results | High to very high | High to extremely high | Usually normal | Usually normal |
| Partial thromboplastin time | Normal to high | High | Normal | Normal |

Anantharaman P, Schmidt RJ, Holley JL. Pregnancy and Renal Disease. Lerma EV, Berns JS, Nissenson AR, editor. McGraw-Hill, New York, 2008, pp. 492-506.

Table 1: The comparative clinical and laboratory features of different critical illnesses related to renal pathologies during the pregnancy

| Clinical parameters | Pre-eclampsia | HELLP | Acute fatty liver of pregnancy | TTP | HUS |
|-------------------------------|-----------------|-----------------|--------------------------------|-----------------|-------------------|
| Typical onset | Third trimester | Third trimester | Third trimester | Third trimester | Postpartum period |
| Hypertension | Common (100%) | Common | Less common | Rare | Usually not |
| Low platelets | ± | 100% | ± | 100% | ± |
| Transaminases | = | +++ | + | = | = |
| Bilirubin | = | + | +++ | + | ++ |
| Hemolytic anemia | = | + | + | ++ | +++ |
| Neurological signs | ± | ± | ± | +++ | ± |
| Fever | = | = | + | + | + |
| Associated with pre-eclampsia | | Common | May be | Rare | Rare, possible |

















Hemolysis, elevated liver enzymes low platelets (HELLP) (Thrombotic thrombocytopenic purpura (TTP), HUS: Hemolytic uremic syndrome



Table 1: The comparative clinical and laboratory features of different critical illnesses related to renal pathologies during the pregnancy

| Clinical parameters | Pre-eclampsia | HELLP | Acute fatty liver of pregnancy | TTP | HUS |
|-------------------------------|-----------------|-----------------|--------------------------------|-----------------|-------------------|
| Typical onset | Third trimester | Third trimester | Third trimester | Third trimester | Postpartum period |
| Hypertension | Common (100%) | Common | Less common | Rare | Usually not |
| Low platelets | ± | 100% | ± | 100% | ± |
| Transaminases | = | +++ | + | = | = |
| Bilirubin | = | + | +++ | + | ++ |
| Hemolytic anemia | = | + | + | ++ | +++ |
| Neurological signs | ± | ± | ± | +++ | ± |
| Fever | = | = | + | + | + |
| Associated with pre-eclampsia | | Common | May be | Rare | Rare, possible |

Clinical characteristics of liver diseases in pregnancy

| Disease | Trimester | | | | Laboratory studies | | | Differential diagnosis | Prognosis |
|--------------------------------|---|---|---|--|---|-------------------|--|---|--|
| | 1 | 2 | 3 | PP | Amino-transferases, U/L | Total bili, mg/dL | Other | | |
| Hyperemesis gravidarum |  |  |  |  | <200 (ALT>AST) may be as high as 1000 | <4 | | Gastroenteritis, cholecystitis, hepatitis, intestinal obstruction, peptic ulcer disease, pancreatitis, appendicitis, diabetic ketoacidosis, hyperparathyroidism, hyperthyroidism, drug toxicity | Maternal and fetal mortality rare; disease may recur. |
| HELLP syndrome |  |  |  |  | <500 (median 250) unless hepatic infarction | ↑ (median 1.5) | PLTS <100,000 LDH >600 | Acute fatty liver of pregnancy, gastroenteritis, hepatitis, pyelonephritis, appendicitis, cholelithiasis, idiopathic thrombocytopenic purpura, hemolyticuremic syndrome | Maternal mortality low, but complications high; fetal mortality may be as high as 35 percent; recurs 3 to 27 percent |
| Intrahepatic cholestasis |  |  |  |  | <500 usually >1000 occasionally | <6 | Bile acids ↑ AP 4x normal (out of proportion to GGT) | Cholelithiasis, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, drug hepatotoxicity | Maternal mortality rare; fetal mortality 1 to 2 percent; associated with prematurity and stillbirth, recurs in 60 to 70 percent. |
| Acute fatty liver of pregnancy |  |  |  |  | <500 may be as high as 1000 | ↑ | WBC ↑ PT ↑ PLTS ↓ glucose ↓ uric acid ↑ | HELLP, drug toxicity, fulminant hepatic failure | Maternal mortality <3 percent; fetal mortality as high as 35 to 45 percent; recurrence uncommon. |

5- TTP

- Although TTP and HUS represent a spectrum of disease that includes MAHA, thrombocytopenia, and AKI, **TTP is more likely to occur in the first trimester**, when the anemia and thrombocytopenia are the predominant features and kidney injury may not be severe.
- Patients may have a **severe deficiency of ADAMTS-13** (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).
- **Plasma exchange** is the primary treatment, along with the use of **high-dose corticosteroids**.